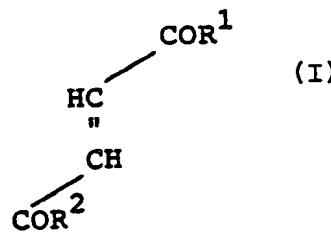


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(54) Title: PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF PSORIASIS



(57) Abstract

The invention comprises compositions and methods for the treatment of psoriasis. The compositions comprise compounds of formula (I).

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PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF PSORIASIS
Background of The Invention

Psoriasis is one of the most widespread chronic diseases. It affects about two percent of the adult white population, the most severe symptoms being shown by patients 5 in the age groups between twenty and fifty years old.

Psoriasis is characterized by a greatly accelerated rate of epidermal turnover. Instead of the normal period of 28 days from the time of cell division in the basal layers until the cell is shed from the stratum 10 corneum, in psoriasis this takes only about four days.

The causes and mechanism of development of psoriasis are unknown, and for this reason a completely effective treatment for this ailment does not yet exist. A great number of approaches have been tried, from the very 15 old, based on natural tars, to the more modern using steroids, sporalene, etc. Tars are messy to apply and have only a limited effect. Their combination with sulfur and salicylic acid are not much better. This therapy is frequently supplemented by the use of ultraviolet (UV) 20 radiation, either natural (sunshine) or artificial (lamps). Other compounds used are: steroids, azaridine, methotrexate, psoralen, and retinoic acid derivatives. All of these have a rather high toxicity and their long term use may result in noxious side effects.

25 A possible approach to the therapy of the disease is to try to influence cellular metabolism, which obviously is much more active in the psoriatic cells than in the normal ones.

30 A few years ago, a new treatment was proposed. This is based on the use of fumaric acid in the form of its simple mono- or diesters or its metal salts, based on the theory that in the psoriatic portions of the skin there exists an unbalance in the dicarboxylic-acids cycle 35 conducive to lower levels of fumarate. This theory seems to be confirmed by the fact that some amino acids, such as glycine, are present in lower quantities in the psoriatic skin, compared to their content in normal skin. Since these

amino acids are also derived from the dicarboxylic-acids cycle, their presence in lower quantities is an added corroboration to the above theory.

A number of patent applications deal with the use of fumarate esters and salts for the treatment of psoriasis. GP 2530372 (13.1.77) describes the use of fumaric acid, fumarate esters, such as monoethyl and monomethyl fumarate, dimethyl fumarate; some salts of the monoesters such as manganese, calcium, zinc, iron, etc. All of these can be mixed with other ingredients such as tartaric acid, citric acid, sugar, and inert fillers. Some of these formulations are for internal use and some for external (topical) application. Related applications, GP 2840498 (10.4.80) and GP 2901452 (17.7.80), describe the addition of glycine, 1-methionine, and 1-cysteine to the above mixtures of fumarate esters and salts. A recent European patent, 01887419 A2 (30.7.86) claims the use of fumarate esters of alcohols having one to eight carbon atoms, esters of higher alcohols (C6-C24), metal salts of the monoesters, and esters of diols, glycerol, and other hydroxyl-containing compounds. Another patent, GP DE 3232883 A1 mentions the preparation of salts of fumaric acid with various caffein-8-ethers. The salts are crystalline and can be used for the preparation of tablets, capsules, etc., in combination with metal salts of fumaric esters, as mentioned before, and also with the optional addition of amino acids such as cysteine and methionine, and of vitamin C.

There exist serious problems as to the use of the above in the therapy of psoriasis. Short-chain fumarate esters are in general irritating materials which frequently produce an unpleasant acidosis effect upon ingestion. Metal salts of the half esters are quickly converted in the stomach into the free acid and the respective metal hydrochloride. The same happens with the caffein-ether salt. The esters are liquid at room temperature and in order to convert them to tablets they have to be adsorbed on, or mixed with, a rather large quantity of inert carrier.

Furthermore, they have a strong characteristic odor and their toxicology has not been studied extensively.

According to a study made with mice, monoethyl fumarate and dimethyl fumarate given per os had an LD₅₀ above 100 mg/kg.

5 Monoethyl fumarate, given intraperitoneally, was more toxic (W. Raab, H&G Nr. 10 (1984)). These fumarate esters are highly irritating to the skin and can produce contact urticaria (Lahty et al., Contact Dermatitis 3, 139-140 (1985)).

10 To summarize: mono and diesters of fumaric acid have been shown to be effective in the treatment of psoriasis, as the experience with several thousand patients indicates (see, for instance: Schafer G. Fumarsauretherapie der Psoriasis, Arztliche Praxis 30, 61 p. 1757-58 (1978); 15 also, Selecta 15, p. 1260-61 (1984)). The esters are irritating to the digestive system and to the skin and their toxicology has not been clearly established; they are also difficult to formulate as tablets.

Recent studies have shown that in psoriatic skin 20 the content of glycine and serine is about twenty-five percent lower than in normal skin (Thaler et al., J. Invest. Dermatol. 75, 156-158 (1980); also, Steinert et al., Biochemistry of Normal and Abnormal Epidermal Differentiation, eds. I.A. Bereinstein and M. Seiji, Tokyo 25 University Press, p. 391-406 (1980)). This deficiency may be related to the fumarate imbalance or to other unknown causes. The addition of glycine as such, to such formulations, cannot contribute much to the therapeutic effect since this water-soluble material will be quickly 30 incorporated into the general metabolic processes, so, at best, its value will be like an added food.

Brief Description of The Invention

We have found that linking amino acids such as glycine, serine, etc., to fumaric acid via a chemical link 35 such as via amide groups, results in conjugates which have a high efficacy in the treatment of psoriasis. The conjugate compounds are mostly stable crystalline solids. They are

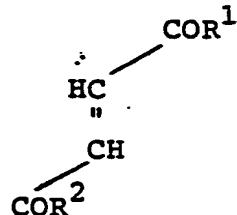
easy to formulate as tablets, ointments, or similar galenic forms. The amide bond is known to be more stable to hydrolysis than an ester group (see, for instance, J. Marach, Advanced Organic Chemistry 3rd ed. p. 339, J. Wiley & Sons, 5 New York (1985)), and therefore the fumar-amido amino acids are converted at a much slower rate into the fumarate and the free amino acid. They are easily absorbed through the digestive system, since it is known that amides have good solubilization properties both with hydrophilic and 10 lipophilic compounds.

In its broadest aspects, therefore, the invention relates to compositions and methods for delivering a residue of fumaric acid and one or more amino acids to humans. It has been found that the compositions of the invention 15 alleviate the symptoms of psoriasis. It has also been found that the compositions of the invention when administered per os have the effect of stimulating digestion and appetite, and when administered per os or topically reduce the tanning effects of the sun.

20 Detailed Description of The Invention

The compounds of the invention include compounds of the formula

25



30 wherein R¹ and R², which are the same or different, each designates

(a) (i) a residue of an amino acid, provided that both R¹ and R² are not residues of glycine,
35 (ii) an ester of an amino acid,
(iii) a salt of an amino acid, or
(iv) a peptide of two or more amino acids, or

(b) a residue of an amino compound selected from the group consisting of lower alkylamines wherein the alkyl group contains up to 10 carbon atoms, alkarylamines, or arylamines, or

5 (c) an OH group, provided that only one of said R¹ and R² may be OH,
or a pharmaceutically acceptable salt thereof.

In accordance with the invention, there are provided fumarate amido-amino acid compounds wherein the 10 amino acids are selected from one or more of: glycine, serine, proline, valine, histidine, methionine, threonine, leucine, isoleucine, cysteine, cystine, methionine, phenylalanine, tyrosine, proline, hydroxyproline, tryptophan, aspartic acid, glutamic acid, histidine, lysine, 15 and arginine, as well as their derivatives, such as esters, salts, etc. Thus, for instance, it is possible to use in the formulations the fumaramide of ethyl glycinate or of sodium glycinate. In other words, it is possible to make use of the carboxylic acid group of the amino acid to 20 further change the solubility and other characteristics of the compound. Furthermore, since fumaric acid has two carboxyl groups, it is possible to prepare and make use of mixed amides, such as the glycine, serine fumaramide.

The amino acid esters of the compounds are 25 desirably lower alkyl esters containing from 1 to 4 carbon atoms in the alkyl group. Where R¹ or R² is an alkylamine, the alkyl group may contain broadly up to 24 carbon atoms, or, more narrowly, up to 10 carbon atoms. By using in the synthesis long-chain amines, it is possible to obtain 30 fumaramides of particular interest for topical use. Suitable compounds are the amides of n-octylamine, 2-ethyl-hexyl amine, dodecylamine, octadecylamine, etc., in the form of simple and mixed diamides, or in combination with the amino acids and substituted amino acids as 35 mentioned above. The introduction of long-chain amines into the molecule makes the resulting materials more lipophilic, and thus enhances the rate of transdermal penetration.

The compositions of the invention may contain the active compounds described above, as well as compounds wherein R¹ and R² are glycine and alkylamine containing up to 24 carbon atoms, together with a pharmaceutically acceptable carrier as are known in the art. The carriers may include vehicles for immediate or sustained release and may be in a variety of dosage forms as are also known in the art.

The methods of the invention include, broadly, a method for delivering residues of fumaric acid and/or amino acids to a patient by administering the compositions of the invention, either per os or topically, as circumstances dictate. The compositions of the invention may be used to alleviate the symptoms of psoriasis. They may also be used to stimulate the appetite, and to reduce the tanning effects of the sun.

The materials of this invention are nonirritating to the skin, and preliminary toxicological studies with the diglycyl fumaramide show the LD₅₀ to be above 10 gr/kg (per os in rats). The diethyl ester of diglycyl fumaramide showed an LD₅₀ above 5 gr/kg. The amide conjugates are mild and nonirritating. Glycine is used in some formulations of aspirin tablets with the object of reducing gastric irritation. Any amount of glycine produced in the stomach by hydrolysis of the amide, will actually act in a beneficial way, in this respect.

The invention is illustrated by the following examples which are not limiting.

EXAMPLES

All quantities are given in parts by weight.

Example 1: = Diglycyl fumaramide (GFA)

Glycine 165 parts, were added to 180 parts of sodium hydroxide dissolved in 720 parts of water. The solution was cooled and to it were added, under stirring, 168 parts of fumaryl chloride. After completion of the reaction, the product was acidified and purified by washing

with water, filtered and dried to obtain the amide acid in the form of a light tan unctuous powder.

M.P. = 260-270°C (dec). N(calc) 12.17%; found: 12.30%.

The material was further characterized by NMR.

5 Example 2: = Lauryl fumaramide (LFA)

Fumaryl chloride 53.2 parts, lauryl (dodecyl) amine 43.3 parts, and 37 parts of sodium hydroxide, in the form of an aqueous solution, were used. The procedure was similar to the one described in Example 1. The product is a 10 soft wax. N(calc.) = 6.20%, found: 6.18%.

10 Example 3: = Serine fumaramide (SFA)

This was similarly made by using serine 8 parts, fumaryl chloride 6.2, and sodium hydroxide 6.65 as a solution in water. The material is waxy, light yellow in 15 color. N(calc.) = 9.6%; found: 9.4%.

15 Example 4: = Glycyl-lauryl fumaramide (GLFA)

Glycine 4.5 parts, dodecylamine 11.1 parts, fumaryl chloride 19.3 parts, and sodium hydroxide 8 parts, as an aqueous solution, were reacted as in Example 1.

20 Obtained an off-white waxy material. N(calc.) 8.2%; found: 7.9%.

20 Example 5: = Ethyl ester of diglycyl fumaramide (EGFA)

Glycine ether ester hydrochloride 13.9 parts, fumaryl chloride 7.65 parts, and 8.8 parts of sodium 25 hydroxide in water were reacted as above. After purification the material obtained is an off-white powder. N(calc.) 9.7; found: 10.1.

GALENIC FORMS

30 Example 6: = Capsules

Pure GFA prepared as per Example 1 was put in gelatin capsules (100mg. each) and these were given to patients suffering from psoriasis, at an initial rate of 3 capsules a day and going up to 8 capsules a day, if necessary, the exact amount depending on the individual 35 patient. After several weeks of this therapy the lesions started to disappear. No side effects were noticed.

Example 7: = Tablets

The same material was granulated with 1% polyvinylpyrrolidinone and 0.2% magnesium stearate and then compressed into tablets. These were hard and nonfriable.

5 Example 8: = Gel

GFA 40 parts, propylene glycol 30, isopropyl myristate 4, cetyl alcohol 6, and ethanol 22, were mixed well. The resulting gel had a viscosity of 30,000 cps (Brookfield). It was packed in tubes and used for the 10 topical treatment of psoriasis patients. After only two weeks of treatment descamation was noticed as well as a beginning of healing.

The same material was used with good results for the treatment of a patient with a localized hyperkeratosis. 15 After about one week of twice a day application, the skin was smooth and free of scales.

Example 9: = Gel

LFA prepared as per Example 2, 38.4 parts were mixed with 12.1 cetyl alcohol, 11.4 isopropyl myristate, 20 11.6 propylene glycol, 20.1 ethanol, and 1.4 silica. The resulting gel was packed in tubes and used for the topical treatment of psoriatic wounds.

Example 10: = Gel

A gel was prepared as described in Example 9 but 25 using the material of Example 4 (GLFA).

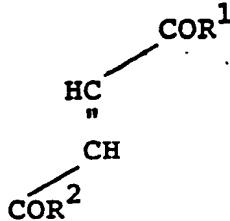
Example 11: = Shampoo

The material of Example 4 (GLFA) has surfactant properties and is a medium foamer. When diluted with water to a 10% concentration it was used as a scalp wash for 30 alleviating psoriatic wounds in that area of the body. At a dilution of 5% it was used as a bath shampoo.

CLAIMS:

1. A compound of the general formula:

5



10 wherein R^1 and R^2 , which are the same or different, each designates a residue of an amino acid, an ester of such amino acid, or a salt of such amino acid, or a residue of an amino compound (alkylamine, alkarylamine, or arylamine) with at least 4 carbon atoms in the case of an alkylamine, where R^1 or R^2 , or both, can designate a peptide of 2 amino acids, and where either R^1 or R^2 can designate -OH.

15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 395 400 405 410 415 420 425 430 435 440 445 450 455 460 465 470 475 480 485 490 495 500 505 510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 615 620 625 630 635 640 645 650 655 660 665 670 675 680 685 690 695 700 705 710 715 720 725 730 735 740 745 750 755 760 765 770 775 780 785 790 795 800 805 810 815 820 825 830 835 840 845 850 855 860 865 870 875 880 885 890 895 900 905 910 915 920 925 930 935 940 945 950 955 960 965 970 975 980 985 990 995 1000 1005 1010 1015 1020 1025 1030 1035 1040 1045 1050 1055 1060 1065 1070 1075 1080 1085 1090 1095 1100 1105 1110 1115 1120 1125 1130 1135 1140 1145 1150 1155 1160 1165 1170 1175 1180 1185 1190 1195 1200 1205 1210 1215 1220 1225 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7. Derivatives of fumaric acid, substantially as hereinbefore described and with reference to any of the Examples.

5 8. A pharmaceutical composition for alleviating the symptoms of psoriasis and other skin diseases, which contains as active ingredient an effective quantity of a compound claimed in any of claims 1 to 7.

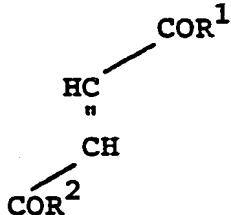
9. A composition as recited in claim 8, for administration per os.

10 10. A composition as recited in claim 8, for topical application.

11. A composition as recited in any of claims 8 to 10, where the active ingredient is selected from monoglycyl fumaramide, diglycyl fumaramide, mono-serine 15 fumaramide, di-serine fumaramide, mono- and diamides of fumaric acid with an alkylamine or with an arylamine, an ester of any of these, or a salt of any salt-forming compounds of these.

12. A compound of the formula:

20



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wherein R¹ and R², which are the same or different, each designates

30 (a) (i) a residue of an amino acid, provided that both R¹ and R² are not residues of glycine,
(ii) an ester of an amino acid,
(iii) a salt of an amino acid, or
(iv) a peptide of two or more amino acids, or
(b) a residue of an amino compound selected from the group consisting of lower alkylamines wherein the alkyl group contains up to 10 carbon atoms, alkarylamines, or arylamines, or

(c) an OH group, provided that only one of such R¹ and R² may be OH,

or a pharmaceutically acceptable salt thereof.

13. A compound as recited in claim 12, where the 5 amino acids are selected from glycine, serine, proline, valine, histidine, methionine, threonine, leucine, isoleucine, cysteine, cystine, methionine, phenylalanine, tyrosine, proline, hydroxyproline, tryptophan, aspartic acid, glutamic acid, lysine, and arginine.

10 14. A compound as recited in claims 12 and 13, where R¹ or R² is an amino acid residue linked to the fumaric acid residue by an amido linkage.

15 15. A compound as recited in claims 12 to 14, where the substituent R¹ or R², or both, each designates a residue of glycine, serine, or a peptide containing a residue of glycine or serine, or both, provided that both R¹ and R² are not residues of glycine.

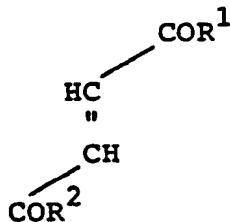
20 16. A compound as recited in any of claims 12 to 15, where the amino acid esters are lower alkyl esters containing from 1 to 4 carbon atoms in the alkyl group.

25 17. A compound selected from group consisting of glycine-serine-fumaramide, di-serine-fumaramide, di-(glycine-serine)-fumaramide, di-(serine-glycine)-fumaramide, glycine-lauryl-fumaramide, the lower alkyl esters of said fumaramides, and the pharmaceutically acceptable salts thereof.

18. The diethyl ester of diglycyl fumaramide.

19. A pharmaceutical composition which contains an active compound of the formula

30



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wherein R¹, and R², which are the same or different, each designates

5 (a) (i) a residue of an amino acid,
(ii) an ester of an amino acid,
(iii) a salt of an amino acid, or
(iv) a peptide of two or more amino acids, or
(b) a residue of an amino compound selected from the group consisting of alkylamines, alkarylamines, or arylamines, or
10 (c) an OH group, provided that only one of such R¹ and R² may be OH,

or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

20. A composition as recited in claim 19, for
15 administration per os.

21. A composition as recited in claim 19, for topical application.

22. A composition as recited in any of claims 19 to 21, where the active ingredient is selected from the group consisting of monoglycyl fumaramide, diglycyl fumaramide, mono-serine fumaramide, di-serine fumaramide, alkylamine or arylamine, mono- and diamides of fumaric acid, esters of any of said compounds, or the pharmaceutically acceptable salts thereof.

25 23. A pharmaceutical composition for stimulating digestion or appetite which contains an active compound of the formula

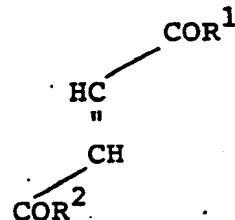


35 wherein R¹, and R², which are the same or different, each designates

(a) (i) a residue of an amino acid,

(ii) an ester of an amino acid,
(iii) a salt of an amino acid, or
(iv) a peptide of two or more amino acids, or
(b) a residue of an amino compound selected from the
5 group consisting of alkylamines, alkarylamin es, or
arylamines, or
(c) an OH group, provided that only one of such R¹ and
R² may be OH,
or a pharmaceutically acceptable salt thereof; and a
10 pharmaceutically acceptable carrier.

24. A pharmaceutical composition for reducing the
tanning effect of exposure to the sun which contains



20 wherein R¹ and R², which are the same or different, each
designates

(a) (i) a residue of an amino acid,
(ii) an ester of an amino acid,
(iii) a salt of an amino acid, or
25 (iv) a peptide of two or more amino acids, or
(b) a residue of an amino compound selected from the
group consisting of alkylamines, alkarylamin es, or
arylamines, or
(c) an OH group, provided that only one of such R¹ and
R² may be OH,
30 or a pharmaceutically acceptable salt thereof; and a
pharmaceutically acceptable carrier.

25. A method for delivering a residue of fumaric
acid and/or one or more amino acids to humans comprising the
35 step of administering a composition as recited in claim 19.

26. A method for the treatment of psoriasis comprising the step of administering to a patient an effective amount of a composition as recited in claim 19.

27. A method as recited in claim 26 wherein said 5 composition is administered per os or topically.

28. A method for stimulating digestion or appetite comprising administering to a patient, per os, an effective amount of a composition as recited in claim 23.

29. A method for reducing the tanning effect of 10 exposure to the sun comprising the step of administering to a patient an effective amount of a composition as recited in claim 24.

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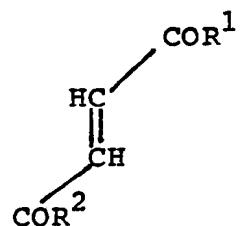
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AMENDED CLAIMS

[received by the International Bureau on 16 February 1989 (16.02.89)
original claims 1-18 cancelled and replaced by new claims 30-41;
claims 19, 22-24 amended; other claims unchanged (7 pages)]

19. A pharmaceutical composition which comprises a pharmaceutically effective amount of a compound of the formula



, or a pharmaceutically acceptable salt thereof, wherein R^1 , and R^2 , which are the same or different, each designates

- (a) (i) a residue of an amino acid or derivative thereof,
- (ii) an ester of an amino acid or derivative thereof,
- (iii) a salt of an amino acid or derivative thereof, or
- (iv) a peptide of two or more amino acids or derivatives thereof or an ester of said peptide, or
- (b) a residue of an amino compound selected from the group consisting of alkylamines, alkarylamines, or arylamines, or
- (c) an OH group, and

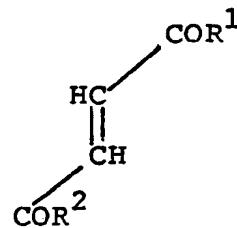
a pharmaceutically acceptable carrier.

20. A composition as recited in claim 19, for administration per os.

21. A composition as recited in claim 19, for topical application.

22. A composition as recited in any of claims 19 to 21, wherein the pharmaceutically effective compound is selected from the group consisting of monoglycyl fumaramide, diglycyl fumaramide, mono-serine fumaramide, di-serine fumaramide, serine-glycine-fumaramide, glycine-serine-fumaramide, di-(serine-glycine)-fumaramide, di-(glycine-serine)-fumaramide, alkylamine or arylamine, a monoamide of fumaric acid, a diamide of fumaric acid, an alkyl mono- or diester of any of said compounds, and a pharmaceutically acceptable salt thereof.

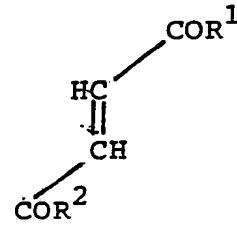
23. A pharmaceutical composition for stimulating digestion or appetite which comprises an amount effective for stimulating digestion or appetite of a compound of the formula



, or a pharmaceutically acceptable salt thereof, wherein R^1 , and R^2 , which are the same or different, each designates

- (a) (i) a residue of an amino acid or derivative thereof,
- (ii) an ester of an amino acid or derivative thereof,
- (iii) a salt of an amino acid or derivative thereof, or
- (iv) a peptide of two or more amino acids or derivatives thereof or an ester of said peptide, or
- (b) a residue of an amino compound selected from the group consisting of alkylamines, alkarylamines, or arylamines, or
- (c) an OH group, and a pharmaceutically acceptable carrier.

24. A pharmaceutical composition for reducing the tanning effect of exposure to the sun which comprises an amount effective for reducing the tanning effect of exposure to the sun of a compound of the formula



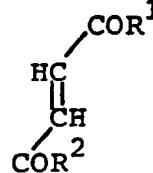
, or a pharmaceutically acceptable salt thereof, wherein R¹ and R², which are the same or different, each designates

- (a) (i) a residue of an amino acid or derivative thereof,
- (ii) an ester of an amino acid or derivative thereof,
- (iii) a salt of an amino acid or derivative thereof, or
- (iv) a peptide of two or more amino acids or derivatives thereof or an ester of said peptide, or
- (b) a residue of an amino compound selected from the group consisting of alkylamines, alkarylamines, or arylamines, or
- (c) an OH group, and a pharmaceutically acceptable carrier.

25. A method for delivering a residue of fumaric acid and/or one or more amino acids to humans comprising the step of administering a composition as recited in claim 19.

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30. A compound of formula



, or a pharmaceutically acceptable salt thereof,
wherein

R^1 and R^2 are the same or different and each is

(a) (i) a residue of an amino acid or derivative thereof provided that only one of R^1 and R^2 is a residue of glycine,

(ii) an ester of an amino acid or derivative thereof provided that only one of R^1 and R^2 is the isopropyl ester of valine,

(iii) a salt of an amino acid or derivative thereof, or

(iv) a peptide of two or more amino acids or derivatives thereof, provided that if R^1 and R^2 are the same peptide, then at least one of the amino acids is different from glycine, or an ester of said peptide, or

(b) a residue of an amino compound selected from the group consisting of an alkylamine, an alkarylamine and an arylamine, or

(c) a hydroxyl group provided that only one of R^1 and R^2 is hydroxyl.

31. A compound as recited in claim 30, wherein the amino acid is selected from the group consisting of glycine, serine, proline, valine, histidine, methionine, threonine, leucine, isoleucine, cysteine, cystine, methionine, phenylalanine, tyrosine, proline, hydroxyproline, tryptophan, aspartic acid, glutamic acid, lysine, and arginine.

32. A compound selected from the group consisting of lauryl fumaramide, mono-serine fumaramide, serine-glycine-fumaramide glycine-serine-fumaramide, di-serine-fumaramide, di-(glycine-serine)-fumaramide, di-(serine-glycine)-fumaramide, glycine-lauryl-fumaramide, an alkyl mono- or diester of any of said compounds, an alkyl ester of mono-glycine fumaramide, an alkyl mono- or diester of di-glycine-fumaramide and a pharmaceutically acceptable salt of any of said compounds.

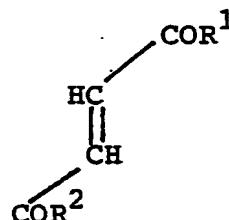
33. A compound as recited in claim 32, wherein said ester is a lower alkyl ester of 1 to 4 carbon atoms.

34. A compound as recited in claim 30, wherein said alkylamine contains up to 24 carbon atoms.

35. A compound as recited in claim 34, wherein said alkylamine is n-octylamine, 2-ethyl-hexyl amine, dodecylamine or octadecylamine.

36. The compound which is the diethyl ester of diglycyl fumaramide.

37. A pharmaceutical composition for alleviating the symptoms of psoriasis and other skin diseases which comprises an amount effective for alleviating the symptoms of psoriasis and other skin diseases of a compound of the formula



, or a pharmaceutically acceptable salt thereof, wherein R^1 , and R^2 , which are the same or different, each designates

- (a) (i) a residue of an amino acid or derivative thereof,
- (ii) an ester of an amino acid or derivative thereof,
- (iii) a salt of an amino acid or derivative thereof, or

- (iv) a peptide of two or more amino acids or derivatives thereof or an ester of said peptide, or
- (b) a residue of an amino compound selected from the group consisting of alkylamines, alkarylamines, or arylamines, or
- (c) an OH group, and

a pharmaceutically acceptable carrier.

38. A composition as recited in claim 37, which is administered per os.

39. A composition as recited in claim 37, which is administered topically.

40. A composition as recited in any of claims 37 to 39, wherein the compound is selected from the group consisting of monoglycyl fumaramide, diglycyl fumaramide, mono-serine fumaramide, di-serine fumaramide, a monoamide of fumaric acid with an alkylamine or with an arylamine, a diamide of fumaric acid with an alkylamine or with an arylamine, an alkyl mono- or diester of any of said compounds and a pharmaceutically acceptable salt of any said compounds.

41. A composition as recited in claim 37, wherein said compound is selected from the group consisting of lauryl fumaramide, mono-glycine fumaramide, mono-serine fumaramide, diglycine fumaramide, diserine fumaramide, glycine-serine-fumaramide, serine-glycine-fumaramide di-(glycine-serine)-fumaramide, di-(serine-glycine)-fumaramide, glycine-lauryl-fumaramide, an alkyl mono- or diester of any of said compounds and a pharmaceutically acceptable salt of any of said compounds.

INTERNATIONAL SEARCH REPORT

International Appln. No PCT/US88/02941

I. CLASSIFICATION

SUSPECT MATTER (if several classification symbols apply, indicate all):

According to International Patent Classification (IPC) or to both National Classification and IPC
 US CL. 560/38,39,40,41,147,153,179; 562/445,446,447,450,556,
 INT. CL. 4th Ed. C07C 101/02, 30,32; C07C 149/20, 149/20;

II. FIELDS SEARCHED

Minimum Documentation Searched *

Classification System	Classification Symbols
	560/38,39,40,41,147,153,179; 562/445,446,447,450,556,564,565; 548/534,344
US Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *	

III. DOCUMENTS CONSIDERED TO BE RELEVANT **

Category *	Citation of Document, * ⁶ with indication, where appropriate, of the relevant passages * ⁷	Relevant to Claim No. *
X	Chemical Abstract, Vol. 93, issued 14 July 1980, (Columbus, Ohio) "Direct gas chromatographic resolution of enantiomers on optically active mesophases. IV. Effect of structure on selectivity and liquid crystal-line behavior". (Lochmueller) abstract no. 17159b.	1-29
X	Chemical Abstract, Vol. 99, issued 21 November 1983, (Columbus, Ohio) "Derivatizing reagents for high-performance liquid chromatography detection of peptides at the picomole level". (Meek) abstract no. 172215j	1-29
X	Chemical Abstract, Vol. 103, issued 08 July 1985, (Columbus, Ohio) "N-Maleyl amino acids and peptides" (Augustin) abstract no. 6698a.	1-29

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"A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search *

14 NOVEMBER 1988

Date of Mailing of this International Search Report *

20 DEC 1988

International Searching Authority *

ISA/US

Signature of Authorized Officer **



ATTACHMENT TO PCT/ISA/210
I. CLASSIFICATION OF SUBJECT MATTER

CONT'D

US. CL. 562/564, 565; 548/534, 344

INT. CL. 4th Ed. C07C 69/66; 101/72,77,72;
C07D 207/00, 233/64

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THIS SHEET)		
Category	Citation of Document, including, where appropriate, of the relevant passages ¹²	Relevant to Claim No ¹³
X	Chemical Abstract, Vol. 105, issued 08 December 1986 (Columbus, Ohio) "Synthesis and opioid antagonist potencies of naltrexamine bivalent ligands with conformationally restricted spacers." (Portoghese) abstract no. 209242m.	1-29
X	Chemical Abstract, Vol. 104, issued 26 May 1986 (Columbus, Ohio) "A spectrophotometric assay for the characterization of the S subsite specificity of α -chymotrypsin". (Schellenberger) abstract no. 182243c.	1-29

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